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Date of Signature and Deposit: 2-14, 2007

  
Sara D. Vinarsky, Reg. No. 48,524

## PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Alan D. Attie  
Donald L. Gillian-Daniel  
Paul W. Bates

Date: Feb. 13, 2007

Serial No.: 09/620,820

Group Art Unit: 1636

Filed: July 21, 2000

Examiner: Celine X. Qian

Title: INHIBITION OF LIPOPROTEIN SECRETION

File No.: 960296.97290

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SECOND SUPPLEMENTAL DECLARATION OF ALAN D. ATTIE  
Under 37 CFR 1.132

Mail Stop Amendment  
Commissioner For Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Alan D. Attie, do hereby state and swear as follows:

1. I am the Alan D. Attie who is one of the inventors of this patent application, and I make this declaration in support of that patent application.

2. I am a professor in the Department of Biochemistry at the University of Wisconsin-Madison. I have worked as a scientist specializing in the general area of lipid metabolism for 30 years. I have published extensively in this area. A copy of my *Curriculum Vitae* is attached as Exhibit A.

3. I have reviewed the above-identified application and understand the nature and scope of the invention claimed therein. I have also reviewed the Office Action issued by the

U.S. Patent and Trademark Office (USPTO) on August 15, 2006 for this application. I understand that currently Claims 1-12 and 17 are rejected as failing to comply with the enablement requirement. Specifically, the Examiner asserts that

"[A]lthough Applicants have demonstrated that delivering a plasmid construct encoding LDLR354 and KDEL can lower LDL level in a mouse deficient of LDLR 48 hours post injection, whether such treatment would result in any therapeutic response in human is still unpredictable because the specification fails to demonstrate whether sustained expression maybe maintained at sufficient level to lower LDL for longer period of time." (See page 5, of the current Office Action).

4. I respectfully disagree with the Examiner's assertion. I note that with technological advancement use of mouse data to forecast a human therapeutic response is more predictable than ever for a variety of reasons. To begin with, the mouse is the most widely used animal model in lipoprotein research (see Breslow, J.L. (1993) *Proc Natl Acad Sci U S A* 90:8314-8318; De Winther, M.P., and Hofker, M.H. (2002) *Curr Opin Lipidol* 13:191-197; and Marschang, P., and Herz, J. (2003) *Semin Cell Dev Biol* 14:25-35). The same broad usage of the mouse is true of virtually all human diseases, even non-metabolic diseases like cancer (Sharpless, N.E., and Depinho, R.A. (2006) *Nat Rev Drug Discov* 5:741-754) and neurodegenerative diseases (Kahle, P.J., and Haass, C. (2001) *Expert Opin Ther Targets* 5:125-132). Specifically, in my laboratory, we have created common inbred mouse strains to replicate the variable susceptibility of all mammals, including human, to diabetes. Mice have been successfully mined for pathways and genes relevant to human diabetes (Clee, S.M., and Attie, A.D. (2007) *Endocr Rev* 28:48-83).

5. Furthermore, it is widely known that by modifying the expression of genes through transgenic technology, mice can be produced that have similar lipoprotein profiles to humans. Indeed, there are more than 10,000 published articles with the words "mouse" and "lipoprotein". Although the lipoprotein profile of other animals, such as the pig and hamster, is more similar to humans than is the mouse profile; the basic biochemical processes, genes, enzymes, and pathways of the mouse are identical to a human. It is also widely known that by modifying the expression of genes through transgenic technology, mice have been produced that do have similar lipoprotein profiles to humans (See Grass, D.S. et al. (1995) *J Lipid Res* 36:1082-1091; Herrera, V.L. et al., (1999) *Nat Med* 5:1383-1389; Masucci-Magoulas, L., et al., (1997) *Science* 275:391-394; and Takahashi, H., et al., (2001) *Biochem Biophys Res Commun* 283:118-123) and also atherosclerotic lesions and heart failure (see

Braun, A., et al., (2002) *Circ Res* 90:270-276 and Zhang, S., et al., (2005) *Circulation* 111:3457-3464) resembling that of humans.

6. Indeed, in the pharmaceutical industry, one of the most important early validation studies of a drug target involves a transgenic mouse where a gene is either knocked out or overexpressed (depending on whether the desired drug is an antagonist or agonist of the target). If the mouse does not show a phenotype replicating the desired therapeutic outcome, then the target is usually deemed invalid. Therefore, I believe that the mouse is a particularly suitable animal model for studying disease in humans, and especially for studying serum cholesterol levels in humans.

7. Next, in response to the Examiner's comments regarding the lack of sustained expression levels beyond 48 hours in mice to lower LDL, I submit that stable integration of genetic material into a genome and sustained expression of the desired protein is achievable. In recent years, the field of gene therapy has undergone dramatic developments with respect to non-viral and viral delivery systems. In regards to viral systems, it is noted that a favored gene therapy approach, using adenovirus, fell into disfavor after the tragic death of a research subject at the University of Pennsylvania. However, since that time, delivery mechanisms such as in non-viral systems have improved to be far more efficient than in the past.

8. I submit that great progress has been made with adeno-associated virus (AAV) (see Warrington, K.H., Jr., and Herzog, R.W. (2006) *Hum Genet* 119:571-603.) This virus has two main advantages over adenovirus. It can support expression for long periods of time; up to years. In addition, it does not cause the inflammatory response that is commonly associated with adenovirus. For example, AAV gene therapy, a human lipoprotein lipase (LPL) variant was given to LPL-deficient mice (See Rip, J., et al. (2005) *Hum Gene Ther* 16:1276-1286). It normalized the dyslipidemia of the mice for more than one year. Preliminary studies were done in human subjects to show that they express the transduced gene in muscle biopsies. These results are a prelude to a clinical trial of its efficacy for lowering lipids in human subjects. Therefore, contrary to the Examiner's assertions, I believe that not only can delivery of the plasmid construct encoding LDLR354 and KDEL lower LDL levels in a mouse deficient of LDLR, but it can also maintain sustained expression in humans at a sufficient level to lower LDL for a longer period of time.

9. I hereby declare all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and the such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Alan D. Attie

Date: 2/13, 2007

## CURRICULUM VITAE

Alan D. Attie

### Date and place of birth

June 18, 1955; New York City

### Education

1976 B.S. Department of Biochemistry, University of Wisconsin-Madison

1980 Ph.D. Department of Biology, University of California-San Diego

### Positions held

1976-1980: Research Assistant, Department of Biology, University of California-San Diego.

1980-1982: Postdoctoral Fellow, Department of Medicine, University of California-San Diego.

1982-1989: Assistant Professor, Departments of Biochemistry & Comparative Biosciences, University of Wisconsin-Madison.

1989-1995: Associate Professor, Departments of Biochemistry & Comparative Biosciences, University of Wisconsin-Madison.

1995-present: Professor, Department of Biochemistry, University of Wisconsin-Madison.

### Honors & awards

1980: "Fellows' Research Award", Annual meeting of the American Association for the Study of Liver Disease, Chicago.

1980-1982: Postdoctoral Fellowship Award, American Liver Foundation.

1984-1989: Shaw Scholar Award.

1987-1992: Established Investigator of the American Heart Association.

1993: Romnes Faculty Fellow Award.

1995: David Rubinstein Memorial Lecturer, Canadian Lipoprotein Conference, Jasper, Alberta.

1998: Dave McClain Research Award, American Heart Association/Wisconsin Affiliate

2000-2002: Vilas Associate Award

2001: Carl J. Norden Distinguished Teaching Award (Honorable Mention) University of Wisconsin-Madison School of Veterinary Medicine

2003: Co-chairman, Atherosclerosis Gordon Conference

2006: Grand Rounds Speaker & Visiting Professor for cardiovascular fellows, Department of Cardiovascular Medicine, Cleveland Clinic.

### Society memberships

- American Society for Biochemistry and Molecular Biology
- Fellow, Arteriosclerosis Council, American Heart Association
- American Diabetes Association

### Study Sections

- American Heart Association/Wisconsin Affiliate (1985-90; 1994-97)
- American Heart Association (National) Lipoprotein, Lipid Metabolism & Epidemiology (1987-90)
- U.S. Dept. of Agriculture, Human Nutritional Requirements Grants (1991)
- State of California Tobacco-related Disease Program (1993)
- NIH Nutrition Study Section; *Ad hoc* (1992)
- NIH Physiological Chemistry Study Section; *Ad hoc* (1996)
- American Heart Association/Midwest Consortium, Chairman of Study Section (1998-1999)
- NIH site visits (1997, 1999)

- NIH RFA: "Development of Phenotypic Screens for Heart, Lung, and Blood Diseases" Chair (2000)
- American Diabetes Association Research Grant Review Panel (2002-2005)
- NIDDK Board of Scientific Counselors (2004-2008).

### Editorial Boards

- *Journal of Clinical Investigation* (2007-2010)
- *Journal of Biological Chemistry* (2002-2007)
- *Journal of Lipid Research* (Associate Editor 07/01/03- present)
- *Diabetes* (2002-2006)
- *Vascular Pharmacology* (2003-present)

### Professional service

- Research Task Force, American Heart Association/Wisconsin Affiliate (1989-90)
- Credentials Committee, Arteriosclerosis Council, American Heart Association (1989-92)
- Program Committee, Arteriosclerosis Council, American Heart Association (1991-94)
- Executive Committee, Arteriosclerosis Council, American Heart Association (1992-95)
- *Ad hoc* reviewer, NIH, NSF, USDA, VA, Canadian Heart Foundation, Canadian MRC, Wellcome Trust, Dutch Heart Foundation grants
- Organizer, 20th Steenbock Symposium: *Molecular Biology of Atherosclerosis* (1990)
- External reviewer, Alberta Heritage Foundation Lipid & Lipoprotein Research Group, University of Alberta, Edmonton (1991)
- External consultant for curriculum development, St. Mary's University, San Antonio, TX (1994)
- Consultant and member of SAB, Xenon Genetics, Vancouver, BC Canada (1999-2003)
- External Advisory Committee, Southwest Foundation for Biomedical Research Program Project on Genetics of Metabolic Syndrome (2006- )
- Organizing Committee for 2007 American Diabetes Association Conference

### Bibliography of publications

1. Attie, A.D., Weinstein, D.B., Freeze, H.H., Pittman, R.C. and Steinberg, D. (1979) Unaltered catabolism of desialylated low density lipoprotein in the pig and in cultured rat hepatocytes. *Biochem. J.* 180:647-654.
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3. Pittman, R.C., Attie, A.D., Carew, T.E. and Steinberg, D. (1979) Tissue sites of degradation of low density lipoprotein: Application of a method for determining the fate of plasma protein. *Proc. Natl. Acad. Sci. USA* 76:5345-5349.
4. Steinberg, D., Pittman, R.C., Attie, A.D., Carew, T.E., Pangburn, S. and Weinstein, D.B. The Role of the Liver in LDL Catabolism. In *Atherosclerosis, Proceedings of the 5th International Symposium on Atherosclerosis*. (Gotto, A.M., Smith, L.C., eds.) (1979) 800-803.
5. Attie, A.D., Pittman, R.C. and Steinberg, D. (1980) Metabolism of native and lactosylated low density lipoprotein: Evidence for two pathways for catabolism of exogenous proteins in rat hepatocytes. *Proc. Natl. Acad. Sci. USA* 77:5923-5927.
6. Drevon, C.A., Attie, A.D., Pangburn, S.H. and Steinberg, D. (1981) Metabolism of homologous and heterologous lipoproteins by cultured rat and human skin fibroblasts. *J. Lipid Res.*, 22:37-46.

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11. Pittman, R.C., Carew, T.E., Glass, C.K., Green, S.R., Taylor, C.A. and Attie, A.D. A (1983) Radioiodinated, intracellularly trapped ligand for determining the sites of plasma protein degradation *in vivo*. *Biochem. J.* 212,791-800.
12. Steinberg, D. Pittman, R.C., Attie, A.D., Carew, T.E., Joy, L. (1983) Uptake and Degradation of Low Density Lipoprotein by Adipose Tissue *In Vivo*. *Adipocyte Obes.: Cell. Mol. Mech.*, [Proc. Int. Conf.] 197-206.
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